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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,087	12/19/2001	Timothy J Fischer	9250-5CTIP4XX	3082

7590 05/24/2005

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 05/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,087	FISCHER ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/17/05; 5/3/05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-21,23-35,37-40,42,43 and 45-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *49,52 and 53* is/are allowed.

6)☒ Claim(s) *1,3-21,23-35,37-40, 42-43, 45-48, 50,51,54 and 55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/3/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on 2/17/05 and 5/3/05 has been entered.

2. Claims 1, 3-21, 23-35, 37-40, 42-43 and 45-55 are pending and are being acted upon in this Office Action.

3. Applicants' statement filed 2/17/05 that applicants will locate complete citations for Downey et al (No 26) and Toh et al (no. 60) cited on Form PTO-1449 filed December 19, 2001 is acknowledged.

4. The references 1-2 cited on PTO 1449, filed 5/3/05, has not been considered and crossed out because a copy of the references was not included in the amendment filed 5/3/05. Further, the Downey et al reference lacks page number.

5. Claim 37 is objected to for depend from canceled claim 36.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

7. Claims 40, 42-43 and 45-48 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step in claim 40 is how the complex formation overtime correlates with the method for diagnosis or monitoring of a hemostatic dysfunction of inflammatory condition.

8. The filing date of the instant claims is deemed to be the filing date of the parent application 09/591,642 filed 6/9/00 because the 09/244,340, 09/001,647, 08/859,773 and 08/477,839 parent applications do not support the claimed limitation "the formation of a complex comprising at least C-reactive protein and at least one human lipoprotein" of the instant application.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 1, 3-21, 23-35, 37-39, 50-51, and 54-55 are rejected under 35 U.S.C. 102(e) as being anticipated by US 6,429,017 B1 (filed Feb 4, 1999) as evident by Ridker et al (Circulation 97: 2007-2011, 1998; PTO 892).

The '017 patent teaches a method of diagnosing hemostatic dysfunction such as disseminated intravascular coagulation with an inflammatory condition (see summary of the invention, col. 3, line 49, claim 29 of '017 patent, in particular) such as infection (see col. 6, Table 1, in particular) or systemic inflammatory response syndrome (SIRS) (see col. 7, line 1-2, in particular). The reference method comprises adding one or more reagents such as calcium, magnesium, manganese, iron or barium or calcium chloride, which are divalent metal ion, to a test sample such as blood or plasma (see col. 11, lines 50-61, col. 12, line 39-40, claims 13-14, 22-23 of '017 patent, in particular) in order to cause formation of a complex comprising C-reactive protein and lipoprotein, measuring the formation of complex over time as to derive a time-dependent measurement profile (see claim 1, part b, claim 5 part b of '017 patent, in particular) and determining the slope (which is rate of change) and/or total change in the time-dependent measurement profile to diagnose hemostatic dysfunction in the patient (see claim 19 part 2 of '017 patent, in particular). The addition of metal divalent cation to the plasma sample causes complex formation between C-reactive protein (CRP) and the human lipoprotein that are already in the patient's plasma sample (see paragraph bridging col. 12 and 13 of '017 patent, in particular). The evidentiary reference Ridker et al teaches C-reactive protein is a sensitive marker of systemic inflammation (see page 2007, col. 1, in particular). Further, the '017 patent teaches

CRP forms complex with lipoprotein such as low density lipoprotein (LDL), very low density lipoprotein (VLDL) (see col. 3, line 1, de Beer reference therein, in particular). Since the blood sample is from a patient such as human, the reference blood sample inherently contains various lipoprotein such as LDL and VLDL and combination thereof. The reference method further comprises a clot inhibitor as part of the reagents such as one or more hirudin, heparin, PPAC, I2581 and antithrombin (see col. 12, line 41, claims 2, 16, 25, 30 of '017 patent, in particular). Claims 8-9 and 12 are included in this rejection because disseminated intravascular coagulation inherently causes death of the patient. The reference also teaches the method is performed in the absence of clot inducing reagents (see claim 5 of '017, col. 11, line 63-64, in particular). The formation of precipitate is measured at least once after time zero wherein the measurements are measured by optical transmission or absorbance (see Figure 1A and 1B, paragraph bridging col. 1 and 2, claim 12 of '017, in particular). A single endpoint measurement can also be made after time zero using latex agglutination assay (see col. 14, line 6-9, in particular). The reference method wherein a single reagent such as calcium is used prior to taking measurement (see col. 1, lines 50-60, in particular). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 2/17/05 and 5/3/05 have been fully considered but are not found persuasive.

Applicants' position is that claims have been amended in view of the examiner's comments and suggestions as a result of April 19, 2005 telephonic interview. Further, Applicants' noted that the '017 patent does not teach every limitation of the claims. The claims of the '017 patent are drawn to a generic method of diagnosing hemostatic dysfunction by adding reagent such as calcium to a test sample.

In response, although the claims have been amended, the amended claims only overcome the enablement, written description and 112 second rejections. In contrast to applicants assertion that the '017 patent does not teach every limitations of the claims, the ingredient such as adding divalent metal ion in the claimed method is taught throughout the '017 patent for diagnosing hemostatic dysfunction comprising inflammatory condition. The formation of complex between C-reactive protein (CRP) and lipoprotein is also known at the time the invention was filed as evident by the teaching of '017 patent and references cited therein. The evidentiary reference Ridker et al teaches C-reactive protein is a sensitive marker of systemic inflammation (see page 2007, col. 1, in particular). The teachings of the '017 have been discussed supra and are incorporated here by reference.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1, 3-21, 23-35, 37-39, 50-51, and 54-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,429,017 B1 (of record, filed Feb 4, 1999) in view of Rowe et al (of record, Clin Exp Immunol 58: 237-244, 1984; PTO 1449) and Ridker et al (Circulation 97: 2007-2011, 1998; PTO 892).

The teachings of the '017 patent have been discussed supra. The '017 patent further teaches that it is desirable to calculate the slope of the waveform prior to initiation of clot formation since specificity and sensitivity are greatly improved and are better than the standard tests used in the diagnosis of haemostatic dysfunction (see col. 9, lines 58 bridging col. 10, lines 1-13, in particular).

The claimed invention differs from the teachings of the reference only in that the method of diagnosing haemostatic dysfunction comprises adding a divalent metal ion to cause formation of a complex (precipitate) comprising at least C-reactive protein and at least one human lipoprotein.

Rowe et al teach human C-reactive forms complex with lipoprotein proteins such as low density lipoprotein (LDL), and very low density lipoprotein (VLDL) in the present of divalent metal ion such as calcium (see page 237, summary, in particular).

Ridker et al teach C-reactive protein is a sensitive marker of systemic inflammation and baseline level of C-reactive protein added to the predictive value of lipid parameters such as total

cholesterol and HDL in determining cardiovascular risk of first myocardial infraction (see page 2007, abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to measure complex formation between C-reactive protein and human lipoproteins as taught by Rowe or Ridker et al for a method of diagnosing haemostatic dysfunction comprising inflammatory condition such as infection and systemic inflammatory response syndrome (SIRS) by adding divalent metal ion to the test sample from a patient with inflammatory condition, measuring the complex overtime to derive a time-dependent measurement profile and determining the slope or change over time and/or total change in precipitation and correlating the increase in steepness of the slope with an increase likelihood of mortality associated with haemostatic dysfunction in the patient as taught by the '017 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Ridker et al teach C-reactive protein is a sensitive marker of systemic inflammation (see page 2007, col. 1, in particular). Rowe et al teach human C-reactive forms complex with lipoprotein proteins such as low density lipoprotein (LDL), and very low density lipoprotein (VLDL) in the present of divalent metal ion such as calcium (see page 237, summary, in particular). The '017 patent teaches it is desirable to calculate the slope of the waveform prior to initiation of clot formation since specificity and sensitivity are greatly improved and are better than the standard tests used in the diagnosis of haemostatic dysfunction (see col. 9, lines 58 bridging col. 10, lines 1-13, in particular).

Applicants' arguments filed 2/17/05 and 5/3/05 have been fully considered but are not found persuasive.

Applicants' position is that one of ordinary skill in the art would not have been motivated to combine these particular references. The '017 patent does not teach the recitations of claim 40 and the cited references do not cure the deficiencies. Applicants respectively submit that it is only through impermissible hindsight combined with picking and choosing portions of the cited references to the exclusions of deficient and/or divergent teachings is one of ordinary skill in the art able to arrive at the present invention recited in claim 40.

In contrast to applicants' assertion that one of ordinary skill in the art would not have been motivated to combine these particular references, the motivation to combine can arise from

the expectation that the prior art elements will perform their expected functions to achieve their expected results when combine for their common known purpose. Section MPEP 2144.07. One having ordinary skill in the art would have been motivated to do this because Ridker et al teach C-reactive protein is a sensitive marker of systemic inflammation (see page 2007, col. 1, in particular). Rowe et al teach human C-reactive forms complex with lipoprotein proteins such as low density lipoprotein (LDL), and very low density lipoprotein (VLDL) in the present of divalent metal ion such as calcium (see page 237, summary, in particular). The '017 patent teaches it is desirable to calculate the slope of the waveform prior to initiation of clot formation since specificity and sensitivity are greatly improved and are better than the standard tests used in the diagnosis of haemostatic dysfunction (see col. 9, lines 58 bridging col. 10, lines 1-13, in particular).

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin , 170 USPQ 209 (CCPA 1971).

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 1, 3-21, 23-35, 37-39, 50-51 and 54-55 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 and 9-19 of U.S. Patent No. 6,429,017 (of record, PTO 892) in view of Rowe et al (of record, Clin Exp Immunol 58: 237-244, 1984; PTO 1449) and Ridker et al (Circulation 97: 2007-2011, 1998; PTO 892).

The '017 patent teaches a method of diagnosing hemostatic dysfunction such as disseminated intravascular coagulation with an inflammatory condition (see summary of the invention, col. 3, line 49, claim 29 of '017 patent, in particular) such as infection (see col. 6, Table 1, in particular) or systemic inflammatory response syndrome (SIRS) (see col. 7, line 1-2, in particular). The reference method comprises adding one or more reagents such as calcium, magnesium, manganese, iron or barium or calcium chloride, which are divalent metal ion, to a test sample such as blood or plasma (see col. 11, lines 50-61, col. 12, line 39-40, claims 13-14, 22-23 of '017 patent, in particular) in order to cause formation of a complex comprising C-reactive protein and lipoprotein, measuring the formation of complex over time as to derive a time-dependent measurement profile (see claim 1, part b, claim 5 part b of '017 patent, in particular) and determining the slope (which is rate of change) and/or total change in the time-dependent measurement profile to diagnose hemostatic dysfunction in the patient (see claim 19 part 2 of '017 patent, in particular). The addition of metal divalent cation to the plasma sample causes complex formation between C-reactive protein (CRP) and the human lipoprotein that are already in the patient's plasma sample (see paragraph bridging col. 12 and 13 of '017 patent, in particular). The evidentiary reference Ridker et al teaches C-reactive protein is a sensitive marker of systemic inflammation (see page 2007, col. 1, in particular). Further, the '017 patent teaches CRP forms complex with lipoprotein such as low density lipoprotein (LDL), very low density lipoprotein (VLDL) (see col. 3, line 1, de Beer reference therein, in particular). Since the blood sample is from a patient such as human, the reference blood sample inherently contains various lipoproteins such as LDL and VLDL and combination thereof. The reference method further comprises a clot inhibitor as part of the reagents such as one or more hirudin, heparin, PPAC, I2581 and antithrombin (see col. 12, line 41, claims 2, 16, 25, 30 of '017 patent, in particular). Claims 8-9 and 12 are included in this rejection because disseminated intravascular coagulation inherently causes death of the patient. The reference also teaches the method is performed in the absence of clot inducing reagents (see claim 5 of '017, col. 11, line 63-64, in particular). The formation of precipitate is measured at least once after time zero wherein the measurements are measured by optical transmission or absorbance (see Figure 1A and 1B, paragraph bridging col. 1

and 2, claim 12 of '017, in particular). A single endpoint measurement can also be made after time zero using latex agglutination assay (see col. 14, line 6-9, in particular). The reference method wherein a single reagent such as calcium is used prior to taking measurement (see col. 1, lines 50-60, in particular).

The claimed invention differs from the teachings of the reference only in that the method of diagnosing haemostatic dysfunction comprising an inflammatory condition comprises adding a divalent metal ion to cause formation of a complex (precipitate) comprising at least C-Reactive protein and at least one human lipoprotein.

The claimed invention differs from the teachings of the reference only in that the method of diagnosing haemostatic dysfunction comprises adding a divalent metal ion to cause formation of a complex (precipitate) comprising at least C-reactive protein and at least one human lipoprotein.

Rowe et al teach human C-reactive forms complex with lipoprotein proteins such as low density lipoprotein (LDL), and very low density lipoprotein (VLDL) in the present of divalent metal ion such as calcium (see page 237, summary, in particular).

Ridker et al teach C-reactive protein is a sensitive marker of systemic inflammation and baseline level of C-reactive protein added to the predictive value of lipid parameters such as total cholesterol and HDL in determining cardiovascular risk of first myocardial infraction (see page 2007, abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to measure complex formation between C-reactive protein and human lipoproteins as taught by Rowe or Ridker et al for a method of diagnosing haemostatic dysfunction comprising inflammatory condition such as infection and systemic inflammatory response syndrome (SIRS) by adding divalent metal ion to the test sample from a patient with inflammatory condition, measuring the complex overtime to derive a time-dependent measurement profile and determining the slope or change over time and/or total change in precipitation and correlating the increase in steepness of the slope with an increase likelihood of mortality associated with haemostatic dysfunction in the patient as taught by the '017 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Ridker et al teach C-reactive protein is a sensitive marker of systemic inflammation (see page 2007, col.

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It is noted that upon indication of allowance, applicants will promptly submit a terminal disclaimer.

16. Claims 49, 52 and 53 are allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

18. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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